IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	Davin MUNN *et al.*	Confirmation No.:	1273
Serial No.:	10/780,150	Group Art Unit:	1628
Filed:	February 17, 2004	Examiner:	Timothy P. THOMAS

For: REGULATION OF T-CELL MEDIATED IMMUNITY BY D ISOMERS OF INHIBITORS OF INDOLEAMINE-2,3-DIOXYGENASE

DECLARATION UNDER 37 C.F.R. §1.132

I, Dr. William Paul Malachowski, declare that:

1. I am an Associate Professor of Chemistry at Bryn Mawr College. I have over 15 years of experience in bioorganic chemistry including enzyme inhibitor design, synthesis and testing. I received a doctorate from the University of Michigan in the field of medicinal chemistry and I am the author of numerous publications (*see* Curriculum Vitae attached as Appendix A). I am a listed inventor on 5 patents/published applications. My work at the Bryn Mawr College involves enzyme inhibitor design including indoleamine-2,3-dioxygenase inhibitor design and synthesis.

2. I am familiar with the above-identified application related to methods of delaying the progression of a tumor comprising administering pharmaceutical compositions containing 1-methyl-D-tryptophan and I have reviewed the Non-Final Office Action dated July 16, 2010. I am also familiar with the references cited against the currently pending claims. In particular, I understand that the Examiner, relying on WO 00/66764, combined with at least Peterson et al. (1994) Med. Chem. Res., 3:531-544. It is my understanding that the Examiner's position

is that since WO 00/66764 teach pharmaceutical uses of racemic 1-methyl-tryptophan, and Peterson teaches separation of racemic 1-methyl-tryptophan into its D- and L-isomers, that it would have been obvious to use the D isomer of 1-methyl-tryptophan for the uses described in WO 00/66764.

3. According to Peterson, the L-isomer is over six-times more effective at inhibiting the indoleamine-2,3-dioxygenase enzyme (*See* Table 1 on page 536 of Peterson). As one of ordinary skill in the art working in the field of synthesis and testing of inhibitors of indoleamine-2,3-dioxygenase for therapeutic use, I would not have been motivated to use the less active D-isomer of 1-methyl-tryptophan for the treatment of cancer based on the teaching of Peterson. On the contrary, based on Peterson, I would have been motivated to use the L-isomer of 1-methyl-tryptophan. I would have not expected, based on Peterson, that the less active D-isomer would be a superior therapeutic composition compared to the L-isomer.

4. I declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: October 26, 2010 Signed: William P. Malachowski

William P. Malachowski Ph.D.

Appendix A

WILLIAM PAUL MALACHOWSKI

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EDUCATION

UNIVERSITY OF MICHIGAN, ANN ARBOR, MI
Ph.D., Medicinal Chemistry, June 1993
M.S., Medicinal Chemistry, December 1988

COLLEGE OF THE HOLY CROSS, WORCESTER, MA
B.A., Chemistry with Honors, May 1987

PROFESSIONAL EXPERIENCE

BRYN MAWR COLLEGE
Associate Professor of Chemistry, 2006-present
Assistant Professor of Chemistry, 2000-2006

UNIVERSITY OF NEW ENGLAND
Assistant Professor of Chemistry, 1996-2000

RENSSELAER POLYTECHNIC INSTITUTE
Post-doctoral Research Assistant with Prof. Arthur G. Schultz, 1993-1996
Accomplished the asymmetric total synthesis of (+)-apovincamine

STATE UNIVERSITY OF NEW YORK AT ALBANY
Lecturer in Organic Chemistry, Fall Semester 1995

UNIVERSITY OF MICHIGAN
Graduate Research Assistant with Prof. James K. Coward, 1987-1993
Synthesised phosphorus-based enzyme inhibitors

GRANT SUPPORT

- National Science Foundation, Major Research Instrumentation Program (Recovery and Reinvestment), "400 MHz NMR Acquisition" (CHE-0958996), 2010-2012 ($263,900)
- National Institutes of Health (National Institute of General Medical Sciences), "Synthetic tools for new antibiotics" (1-R15-GM087291-01A1), 2010-2012 ($211,052)
- American Chemical Society PRF 2008 Supplement for Underrepresented Minority Research Fellowship ($5,000)
- Bristol-Myers Squibb 2007 Undergraduate Research Award in Organic Chemistry ($5,000)
- Pennsylvania Department of Health, Commonwealth Universal Research Enhancement (CURE) Program, "New Tools for the Synthesis of Cyanthiwigin AC and Analogs" 2006 ($9,544)
- Bristol-Myers Squibb 2006 Undergraduate Research Award in Organic Chemistry ($5,000)
- American Chemical Society, The Petroleum Research Fund, "Sequential Birch reduction-allylation/Cope rearrangement for the enantioselective construction of carbocyclic quaternary stereogenic centers" (43238-AC1) 2005-2008 ($80,000)

- National Institutes of Health (National Cancer Institute), "IDO Inhibitors for Combinatorial Cancer Therapy" (R01-CA109542), a collaboration with Lankenau Institute of Medical Research, 2005-8 ($231,000)
- Bristol-Myers Squibb 2004 Undergraduate Research Award in Organic Chemistry ($5,000)
- National Institutes of Health-Academic Research Enhancement Award, "The Asymmetric Synthesis of α-Aminophosphonic Acids" (1-R15-GM58469-01), 1999-2003 ($75,000)
- Pfizer 2002 Summer Undergraduate Research Fellowship Award (mentor to Rachel Kahn) ($5,000)
- Bristol-Myers Squibb 2002 Undergraduate Research Award in Organic Chemistry ($5,000)
- Bristol-Myers Squibb 2001 Undergraduate Research Award in Organic Chemistry ($5,000)
- National Science Foundation-Research at Undergraduate Institutions, "Design, Synthesis and Evaluation of a Novel Serine Protease Inhibitor Based on Monocyclic β-Lactams" (CHE-9710479), 1997-2001 ($54,000)

PUBLICATIONS

- "Enantioselective synthesis of bicarbocyclic structures with an all-carbon quaternary stereocenter through sequential cross metathesis and intramolecular Rauhut–Currier reaction" Yuan Qiao, Sanjeev Kumar, and William P. Malachowski. *Tetrahedron Letters* **2010**, *51(19)*, 2636-2638.
- Sanjeev Kumar, Daniel Jaller, Bhumika Patel, Judith M. LaLonde, James B. DuHadaway, William P. Malachowski, George C. Prendergast and Alexander J. Muller. Structure Based Development of Phenyl-imidazole-derived Inhibitors of Indoleamine 2,3-Dioxygenase. *J. Med. Chem.* **2008**, *51(16)*, 4968-4977.
- "Indoleamine 2,3-Dioxygenase Is the Anticancer Target for a Novel Series of PotentNaphthoquinone-Based Inhibitors" Sanjeev Kumar, William P. Malachowski, James B. DuHadaway, Judith M. LaLonde, Patrick J. Carroll, Daniel Jaller, Richard Metz, George C. Prendergast, and Alexander J. Muller. *J. Med. Chem.* **2008**, *51(6)*, 1706-1718.
- "A key *in vivo* antitumor mechanism of action of natural product-based brassinins is inhibition of indoleamine 2,3-dioxygenase" T. Banerjee, J.B. DuHadaway, P. Gaspari, E. Sutanto-Ward, D.H. Munn, A.L. Mellor, W.P. Malachowski, G.C. Prendergast and A.J. Muller. *Oncogene* **2008**, *27(20)*, 2851-2857.
- "The Enantioselective Synthesis of (-)-Lycoramine with the Birch-Cope Sequence" William P. Malachowski, Tapas Paul, and Sophia Phounsavath. *J. Org. Chem.* **2007**, *72(18)*, 6792-6796.
- "Exploration of the Enantioselective Birch-Cope Sequence for the Synthesis of Carbocyclic Quaternary Stereocenters" Tapas Paul, William P. Malachowski, and Jisun Lee. *J. Org. Chem.* **2007**, *72(3)*, 930-937.
- "The Enantioselective Birch-Cope Sequence for the Synthesis of Carbocyclic Quaternary Stereocenters. Application to the Synthesis of (+)-Mesembrine" Tapas Paul, William P. Malachowski, and Jisun Lee. *Org. Lett.* **2006**, *8(18)*, 4007-4010.
- "Structure-Activity Study of Brassinin Derivatives as Indoleamine 2,3-Dioxygenase Inhibitors" Paul Gaspari, Tinku Banerjee, William P. Malachowski, Alexander J. Muller, George C. Prendergast, James DuHadaway, Shauna Bennett and Ashley Donovan. *J. Med. Chem.* **2006**, *49(2)*, 684-692
- "A New Cancer Immunosuppression Target Indoleamine 2,3-Dioxygenase (IDO). A Review of the IDO Mechanism, Inhibition and Therapeutic Applications" William P. Malachowski, Richard Metz, George C. Prendergast and Alexander J. Muller. *Drugs of the Future* **2005**, *30(9)*, 897-909.
- "A General Strategy for the Synthesis of Azapeptidomimetic Lactams" Robert L. Broadrup, Bei Wang and William P. Malachowski. *Tetrahedron* **2005**, *61(43)*, 10277-10284.
- "IDO In Cancer: Targeting Pathological Immune Tolerance With Small Molecule Inhibitors" Alexander J. Muller, William P. Malachowski, and George C. Prendergast. *Expert Opinion on Therapeutic Targets* **2005**, *9(4)*, 831-49.
- "Sequential Birch Reduction-Allylation and Cope Rearrangement of o-Anisic Acid Derivatives" William P. Malachowski and Marisha Banerji. *Tet. Lett.* **2004**, *45(44)*, 8183-5.
- "The Synthesis of Azapeptidomimetic beta-Lactam Molecules as Potential Protease Inhibitors" William P. Malachowski, Chenyang Tie, Katherine Wang and Robert L. Broadrup. *J. Org. Chem.* **2002**, *67(25)*, 8962-9.

- "Asymmetric Total Synthesis of (+)-Apovincamine and a Formal Synthesis of (+)-Vincamine. Demonstration of a Practical 'Asymmetric Linkage' between Aromatic Carboxylic Acids and Acyclic Substrates" Arthur G. Schultz, William P. Malachowski, and You Pan. *J. Org. Chem.* **1997**, *62(5)*, 1223.
- "The Chemistry of Phosphapeptides: Formation of Functionalized Phosphonochloridates Under Mild Conditions and Their Reaction with Alcohols and Amines" William P.Malachowski and James K. Coward. *J.Org.Chem.* **1994**, *59(25)*, 7616.
- "The Chemistry of Phosphapeptides: Investigations on the Synthesis of Phosphonamidate, Phosphonate, and Phosphinate Analogues of Glutamyl-γ-Glutamate" William P. Malachowski and James K. Coward. *J.Org.Chem.* **1994**, *59(25)*, 7625.
- "Nature of the Rate-determining Steps of the Reaction Catalyzed by the *Yersinia* Protein-tyrosine Phosphatase" Zhong-Yin Zhang, William P. Malachowski, Robert L. Van Etten, and Jack E. Dixon. *J. Biol. Chem.* **1994**, *269(11)*, 8140.

PATENTS

- "Imidazole derivatives as IDO inhibitors and their preparation, pharmaceutical compositions and use in the treatment of diseases" Mario R. Mautino, Sanjeev Kumar, Firoz Jaipuri, Jesse Waldo, Tanay Kesharwani, Nicholas N Vahanian, Charles J. Link, Judith Lalonde, George Prendergast, Alexander Muller, William Malachowski. PCT Int. Appl., WO 2009132238 A2 20091029 **2009**.
- "Preparation of benzochromenedione derivatives for use as IDO inhibitors" George C. Prendergast, William P. Malachowski, Alexander J. Muller. PCT Int. Appl. WO 2008115804 **2008**.
- "Dithiocarbamates as IDO inhibitors and their preparation, pharmaceutical compositions and their use in the treatment of diseases" James B. Duhadaway, George C. Prendergast, William P. Malachowski, Alexander J. Muller. WO 2007050963 **2007**.
- "Novel IDO (indoleamine 2,3-dioxygenase) inhibitors and methods of use" George C. Prendergast, Alexander J. Muller, James B. Duhadaway, and William P. Malachowski. WO 2004094409 **2004**.
- "Novel methods for the treatment of cancer and viral infections" George C. Prendergast, Alexander J. Muller, James B. Duhadaway, and William P. Malachowski. WO 2004093871 **2004**.

PRESENTATIONS

- "IDO in Sickness and in Health: Promoting Antitumor Immune Response" William P. Malachowski. Wesleyan University, October 15, 2010. An invited lecture.
- "The application of the sequential Birch reduction-allylation/Cope rearrangement to the first enantioselective synthesis of (-)-lycoramine" William P. Malachowski, Tapas Paul, Jisun Lee and Sophia Phounsavath. Gordon Research Conference: Natural Products, July 22-27, 2007.
- "The development of highly potent indoleamine 2,3-dioxygenase (IDO) inhibitors with a pyranonaphthoquinone structure" Sanjeev Kumar, James DuHadaway, Judith LaLonde, William Malachowski, Alex Muller, and George Prendergast. 39th ACS Middle Atlantic Regional Meeting, Ursinus College, May 16-18, 2007.
- "The application of the sequential Birch reduction-allylation/Cope rearrangement to the first enantioselective synthesis of (-)-lycoramine" William P. Malachowski, Tapas Paul, and Sophia Phounsavath. 39th ACS Middle Atlantic Regional Meeting, Ursinus College, May 16-18, 2007.
- "The Enantioselective Birch-Cope Sequence for the Synthesis of Cyclohexyl Quaternary Stereocenters" Tapas Paul, William P. Malachowski and Jisun Lee. Gordon Research Conference: Organic Reactions and Processes, July 16-21, 2006.
- "IDO in Sickness and in Health: Promoting Antitumor Immune Response" William P. Malachowski. The Second Annual Leroy B. Townsend Lecture in Medicinal Chemistry, The University of Michigan, Department of Medicinal Chemistry, May 18, 2006. An invited lecture sponsored by the Leroy B. Townsend Medicinal Chemistry Graduate Students Fund at the University of Michigan, Department of Medicinal Chemistry.
- "Development of Brassinin Derivatives as IDO Inhibitors for Combinatorial Cancer Treatment" Alex J. Muller, Tinku Banerjee, James B. Duhadaway, E. Sutano-Ward, Paul Gaspari, William P.

Malachowski, George C. Prendergast. 97th annual meeting of the American Association for Cancer Research, Washington, D.C., April 1-5, 2006.

- "Synthesis of Tryptophan Analogs as Indoleamine 2,3-Dioxygenase (IDO) Inhibitors" Shauna Bennett and William P. Malachowski. Undergraduate Science Research Synposium, Haverford College, October 29, 2005.
- "Synthesis of Brassilexin Derivatives as Indoleamine 2,3-Dioxygenase (IDO) Inhibitors" Ronke Imbeah-Ampiah and William P. Malachowski. Undergraduate Science Research Synposium, Haverford College, October 29, 2005.
- "Sequential Birch reduction-allylation and Cope rearrangement of *o*-anisic acid derivatives" Jisun Lee and William P. Malachowski. Undergraduate Science Research Synposium, Haverford College, October 29, 2005.
- "A General Strategy for the Synthesis of Azapeptidomimetic Lactams" William P. Malachowski, Robert L. Broadrup, Bei Wang, Chenyang Tie, and Katherine Wang. Gordon Research Conference: Heterocyclic Compounds, July 3-8, 2005.
- "Sequential Birch Reductin-Allylation/Cope Rearrangement for the Enantioselective Construction of Carbocyclic Quaternary Stereogenic Centers" William P. Malachowski. 37th ACS Middle Atlantic Regional Meeting, Rutgers University, May 22-25, 2005.
- "Sequential Birch Reduction-Allylation/Cope Rearrangement for the Enantioselective Construction of Carbocyclic Quaternary Stereocenters" William P. Malachowski. Temple University Chemistry Department Seminar, March 31, 2005.
- "Synthesis of Thiohydantoin Tryptophan Derivatives as Indoleamine 2,3-Dioxygenase Inhibitors" Ronke Imbeah-Ampiah and William P. Malachowski. Undergraduate Science Research Synposium, Haverford College, Novermber 6, 2004.
- "The Synthesis of Hemiaminals as Potential Protease Inhibitors" Marisha Banerji and William P. Malachowski. Undergraduate Science Research Synposium, Haverford College, Novermber 6, 2004.
- "Cope Rearrangement of Birch Reduction-Allylation Products" William P. Malachowski and Marisha Banerji. 228th ACS Natioinal Meeting, Philadelphia, August 22-26, 2004.
- "Design and Synthesis of Peptide Hemiaminals as Protease Inhibitors" Tina Morgan Ross and William P. Malachowski. 228th ACS National Meeting, Philadelphia, August 22-26, 2004.
- "Synthesis of Azapeptide Analogues of Freidinger Dipeptide Lactams" Robert L. Broadup and William P. Malachowski. 228th ACS National Meeting, Philadelphia, August 22-26, 2004.
- "Cope Rearrangement of Birch Reduction-Allylation Products" William P. Malachowski and Marisha Banerji. Gordon Research Conference: Natural Products, July 25-30, 2004.
- "The Design and Synthesis of Peptide Hemiaminals as Protease Inhibitors" Tina Morgan Ross and William P. Malachowski. 15th Annual St. Joseph's University Sigma Xi Student Research Symposium, April 23, 2004.
- "The Synthesis of Thiohydantoin Derivatives of Tryptophan as Indoleamine 2,3-Dioxygenase Inhibitors" Sook Chan and William P. Malachowski. 15th Annual St. Joseph's University Sigma Xi Student Research Symposium, April 23, 2004.
- "The Design and Synthesis of Peptidomimetic Monocyclic Beta-Lactam Molecules as Potential Inhibitors of Protease Enzymes" William P. Malachowski, Bei Wang, Chenyang Tie, Katherine Wang, Robert L. Broadrup, and Lauren Abrardo. Gordon Research Conference: Proteolytic Enzyme and Their Inhibitors, July 7-12, 2002.
- "Development of a Novel Method for α-Alkyl-α-amino Phosphonic Acid Synthesis" William P. Malachowski and Kristopher M. Paolino. 221st ACS Naional Meeting, San Diego, April 2001.
- Synthesis of a Serine Protease Inhibitor Based on Monocyclic β-Lactams" William P. Malachowski and Lauren A. Abrardo. 221st ACS National Meeting, San Diego, April 2001.
- "The Synthesis of Monocyclic Beta-Lactam Inhibitors as Serine Protease Inhibitors" William P. Malachowski. Haverford College Chemistry Department Seminar. March 28, 2001.
- "Design, Syntheses and Structure-activity Relationship Study of Phosphapeptide Inhibitors of Glutathionylspermidine Synthetase." Shoujun Chem, Chun-Hung Lin,,David S. Kwon, William P.

Malachowski, Christopher T. Walsh, James K. Coward. 213th ACS National Meeting, San Francisco, April 13-17, 1997.

PROFESSIONAL ORGANIZATIONS

- American Chemical Society member, 1987-present
- Philadelphia Organic Chemists Club, chair-elect, 2007-2008, chair, 2008-2009
- Philadelphia Organic Chemists Club, 2000-present
- Council on Undergraduate Research member, 1997-2003, 2006-present, Institutional Representative, 1998-2000

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